Data and Safety Monitoring

Some Recent Conundrums

Cardiology Research Rounds

June 10, 2024

DSMB Responsibilities

1. Protect the interests of trial participants by:
    a. Monitoring for adverse events
    b. Monitoring for unexpected harm
2. Identify whether the trial has achieved its prespecified goals before the scheduled end of the study
3. Determine if the trial will be unable to demonstrate the anticipated difference between therapies “futility”
4. Monitor trial discipline/rigour

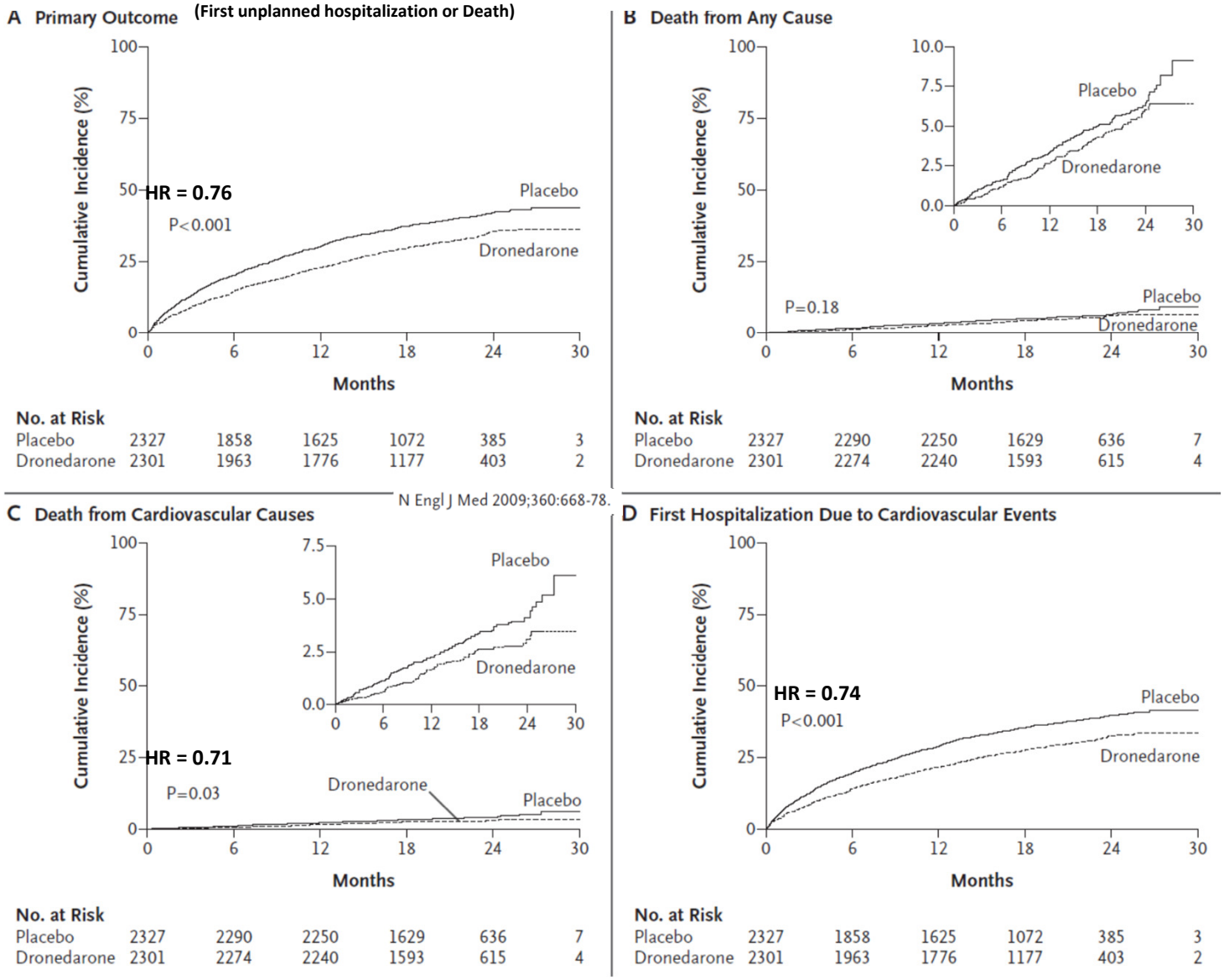
Dronedarone in High-Risk Permanent Atrial Fibrillation

Stuart J. Connolly, M.D., A. John Camm, M.D., Jonathan L. Halperin, M.D., Campbell Joyner, M.D., Marco Alings, M.D., John Amerena, M.D., Dan Atar, M.D., Álvaro Avezum, M.D., Per Blomström, M.D., Martin Borggrefe, M.D., Andrzej Budaj, M.D., Shih-Ann Chen, M.D., Chi Keong Ching, M.D., Patrick Commerford, M.D., Antonio Dans, M.D., Jean-Marc Davy, M.D., Etienne Delacrétaz, M.D., Giuseppe Di Pasquale, M.D., Rafael Diaz, M.D., Paul Dorian, M.D., Greg Flaker, M.D., Sergey Golitsyn, M.D., Antonio Gonzalez-Hermosillo, M.D., Christopher B. Granger, M.D., Hein Heidbüchel, M.D., Josef Kautzner, M.D., June Soo Kim, M.D., Fernando Lanas, M.D., Basil S. Lewis, M.D., Jose L. Me[N Engl J Med 2011;365:2268-76.]lorillo, M.D., Jan Murin, M.D., Calambur Narasimhan, M.D., Ernesto Paolasso, M.D., Alexander Parkhomenko, M.D., Nicholas S. Peters, M.D., Kui-Hian Sim, M.D., Martin K. Stiles, M.D., Supachai Tanomsup, M.D., Lauri Toivonen, M.D., János Tomcsányi, M.D., Christian Torp-Pedersen, M.D., Hung-Fat Tse, M.D., Panos Vardas, M.D., Dragos Vinereanu, M.D., Denis Xavier, M.D., Jun Zhu, M.D., Jun-Ren Zhu, M.D., Lydie Baret-Cormel, M.D., Estelle Weinling, Pharm.D., Christoph Staiger, M.D., Salim Yusuf, M.D., Susan Chrolavicius, R.N., B.A., Rizwan Afzal, M.Sc., and Stefan H. Hohnloser, M.D., for the PALLAS Investigators*

N Engl J Med 2011;365:2268-76.

ATHENA
Dronederone vs
Placebo in AF.
Connolly et al

N Engl J Med 2009;360:668-78.



PALLAS

Permanent Atrial fibriLLAtion outcome Study using Dronedarone on top of standard therapy

A randomized, double blind, placebo controlled, parallel group trial for assessing the clinical benefit of Dronedarone 400 mg BID on top of standard therapy in patients with permanent atrial fibrillation and additional risk factors

Study Objectives

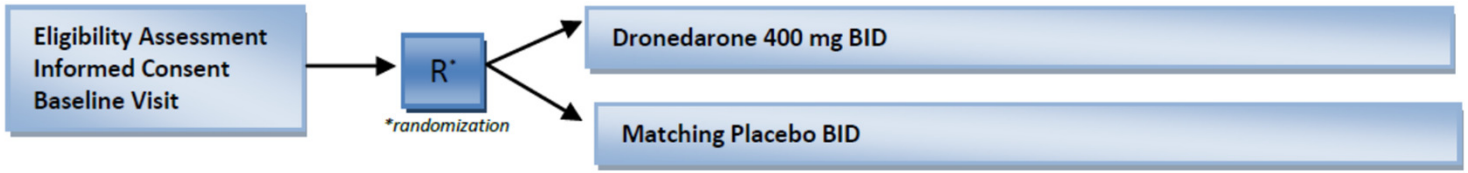
To demonstrate the efficacy of Dronedarone in preventing major cardiovascular events (stroke, systemic arterial embolism, MI or CV Death) or CV hospitalization or death from any cause in patients with permanent atrial fibrillation and additional risk factors.
To demonstrate the efficacy of Dronedarone in preventing cardiovascular death in this patient population and to assess that Dronedarone is well tolerated.

Study Outcomes

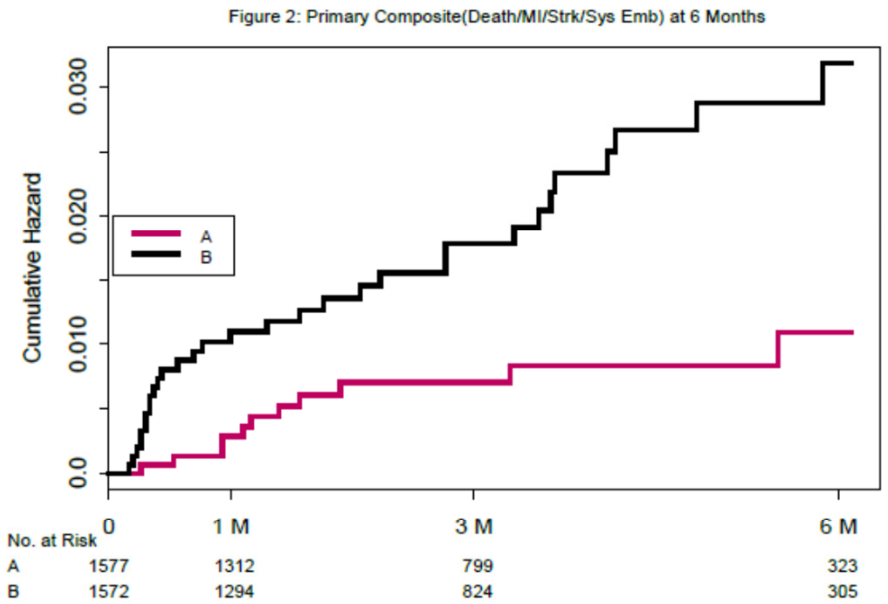
1st Co-primary: Composite endpoint of first stroke, systemic arterial embolism, MI, CV death
2nd Co-primary: Composite endpoint of first CV hospitalization or death from any cause

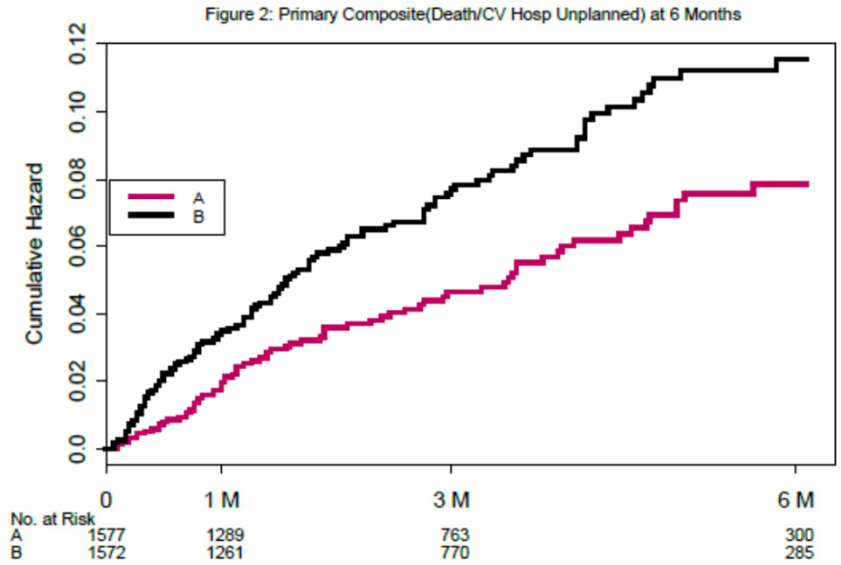
Study Design

Prospective, randomized, double blind, parallel group, international, multicenter trial evaluating the effects of dronedarone 400 mg BID versus placebo in patients with permanent atrial fibrillation and additional risk factors. 10,800 patients will be randomized over 2 years and all patients will be followed to a common study end date (~ August 2013).

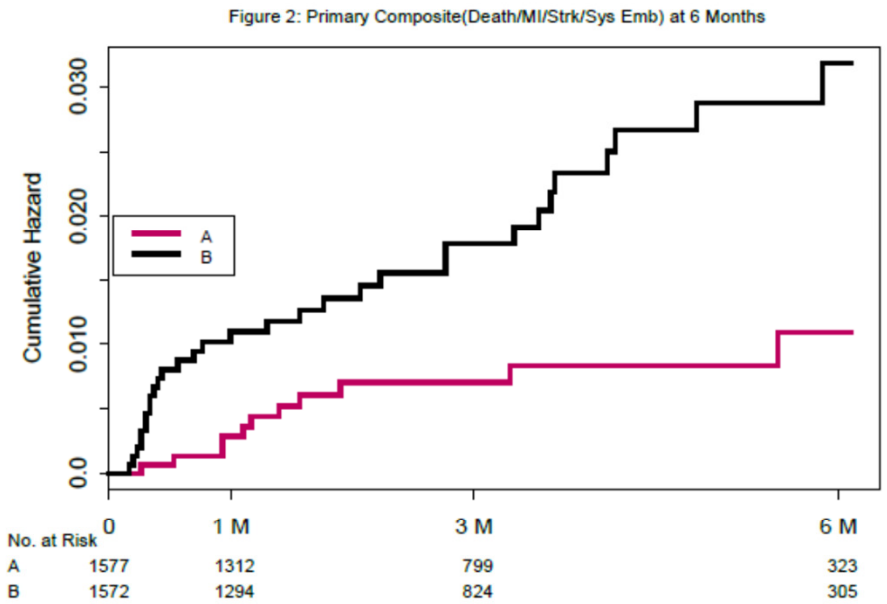


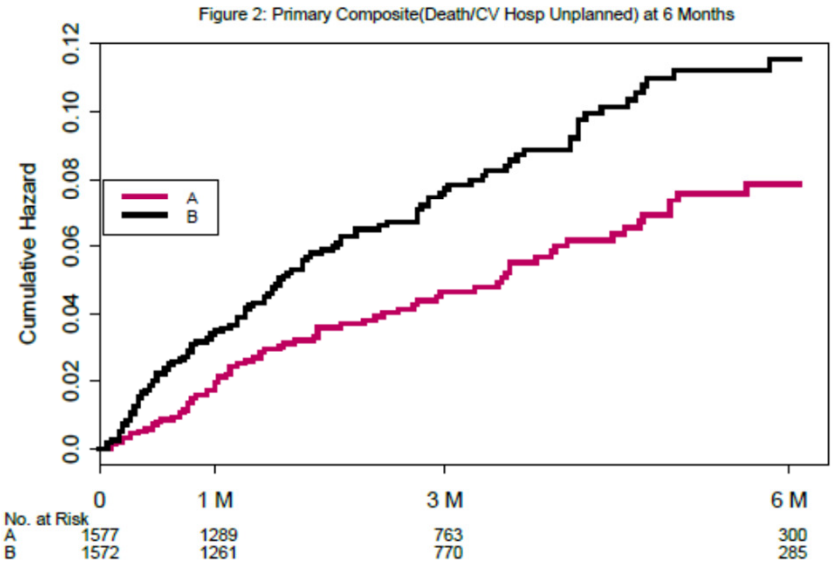
Planned enrollment : 10,800





DSMB meetings March – July 2011

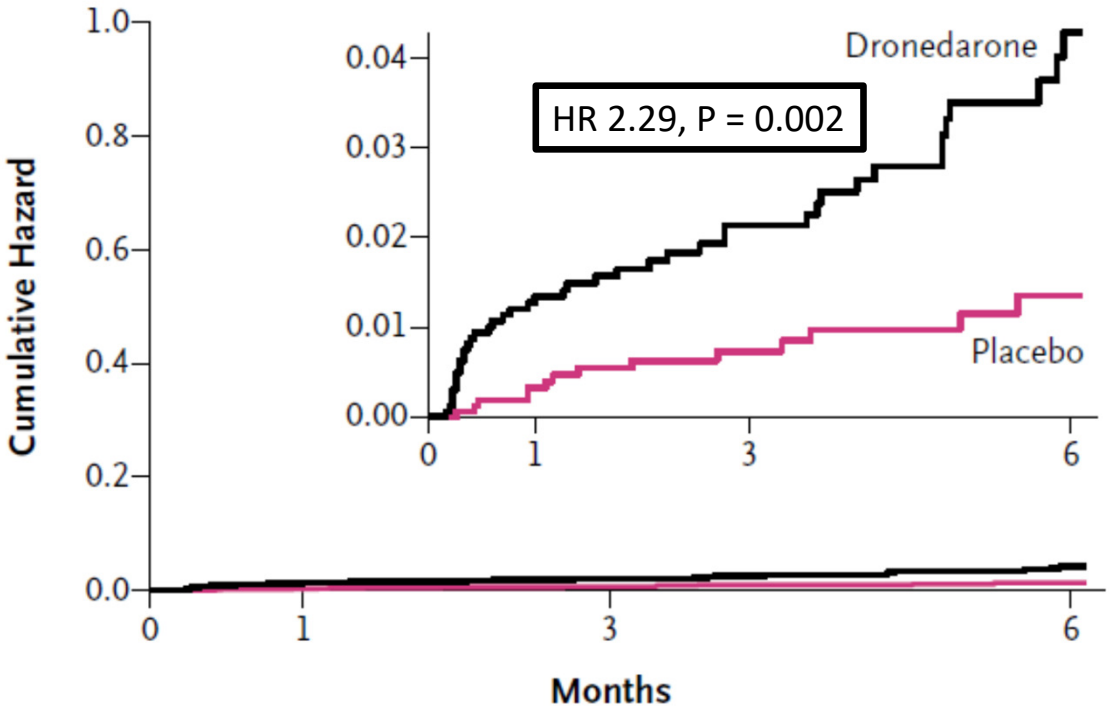




Dronederone

Placebo

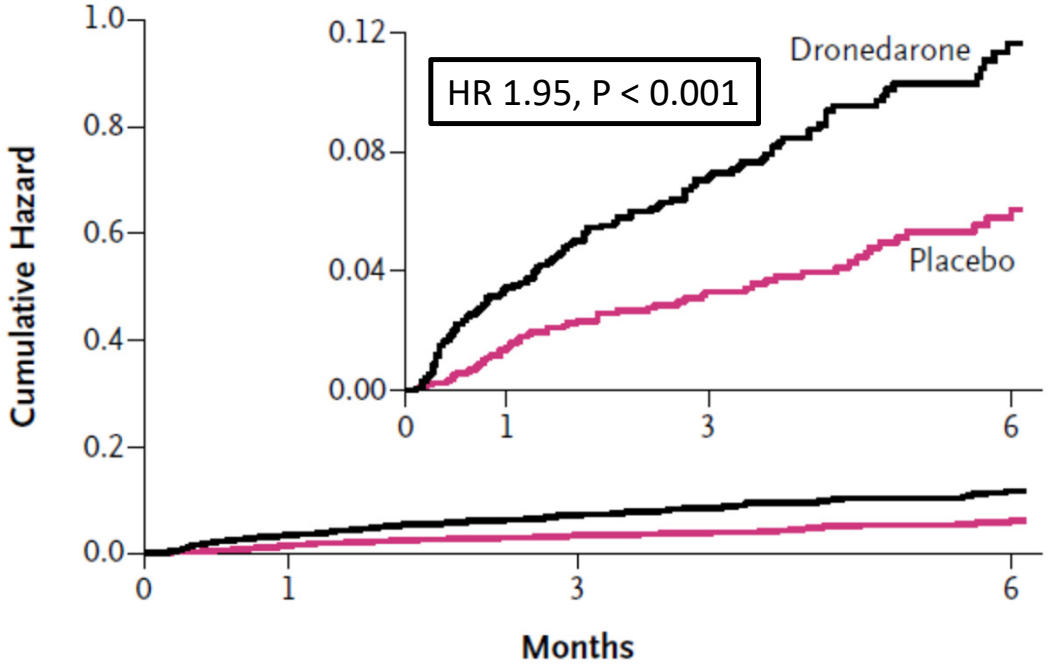
DSMB meeting July 2011.
Termination of study recommended with 3236 Patients enrolled.



No. at Risk				
Placebo	1617	1445	908	377
Dronedarone	1619	1421	930	353

Figure 1. Risk of the First Coprimary Outcome (Stroke, Myocardial Infarction, Systemic Embolism, or Death from Cardiovascular Causes).

PALLAS Trial. Connolly et al. NEMJ 2011; 365: 2268



No. at Risk				
Placebo	1617	1429	882	361
Dronedarone	1619	1389	879	334

Figure 2. Risk of the Second Coprimary Outcome (Unplanned Hospitalization for Cardiovascular Causes or Death).

PALLAS Trial. Connolly et al. NEMJ 2011; 365: 2268

COMPASS

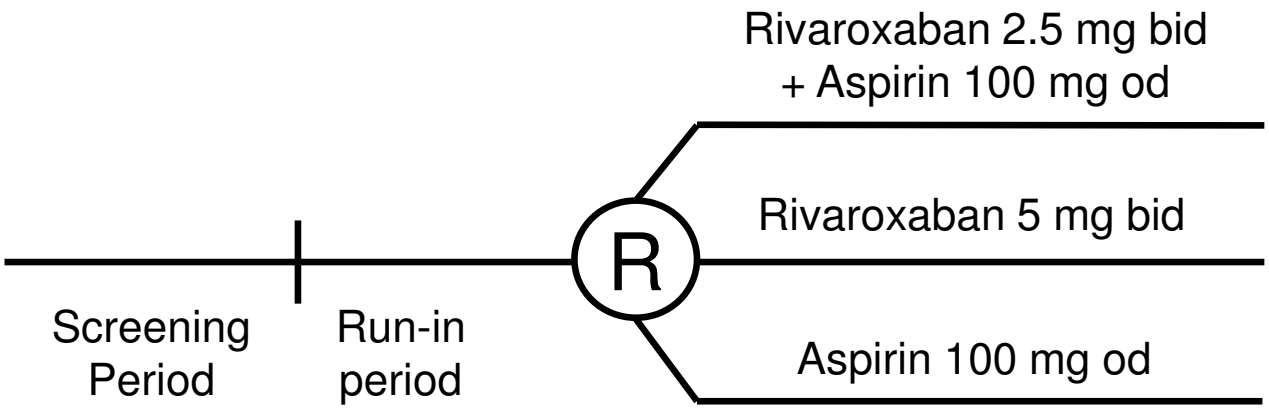
Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease

J.W. Eikelboom, S.J. Connolly, J. Bosch, G.R. Dagenais, R.G. Hart, O. Shestakovska, R. Diaz, M. Alings, E.M. Lonn, S.S. Anand, P. Widimsky, M. Hori, A. Avezum, L.S. Piegas, K.R.H. Branch, J. Probstfield, D.L. Bhatt, J. Zhu, Y. Liang, A.P. Maggioni, P. Lopez-Jaramillo, M. O'Donnell, A. Kakkar, K.A.A. Fox, A.N. Parkhomenko, G. Ertl, S. Stork, M. Keltai, L. Ryden, N. Pogosova, A.L. Dans, F. Lanas, P.J. Commerford, C. Torp-Pedersen, T.J. Guzik, P.B. Verhamme, D. Vinereanu, J.-H. Kim, A.M. Tonkin, B.S. Lewis, C. Felix, K. Yusoff, P.G. Steg, K.P. Metsarinne, N. Cook Bruns, F. Misselwitz, E. Chen, D. Leong, and S. Yusuf, for the COMPASS Investigators*

N Engl J Med 2017;377:1319-30.

COMPASS design

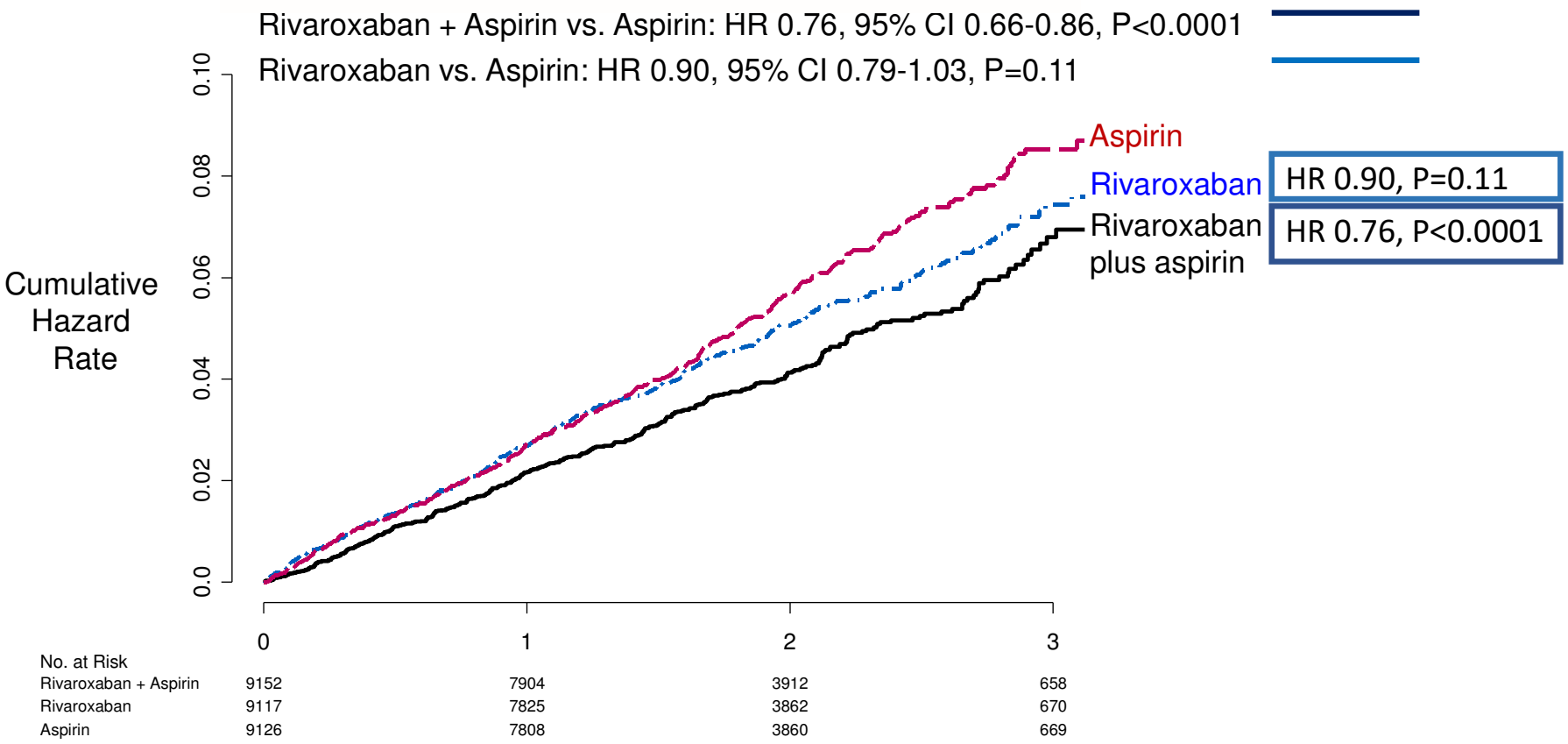
Stable CAD or PAD, planned enrolment 27,400
Event driven, 2,200 participants with a primary outcome event



Primary outcome: CV death, stroke, MI
Expected mean follow up: 3-4 years

Bosch J, et al. Can J Cardiol 2017;33:1027-35.

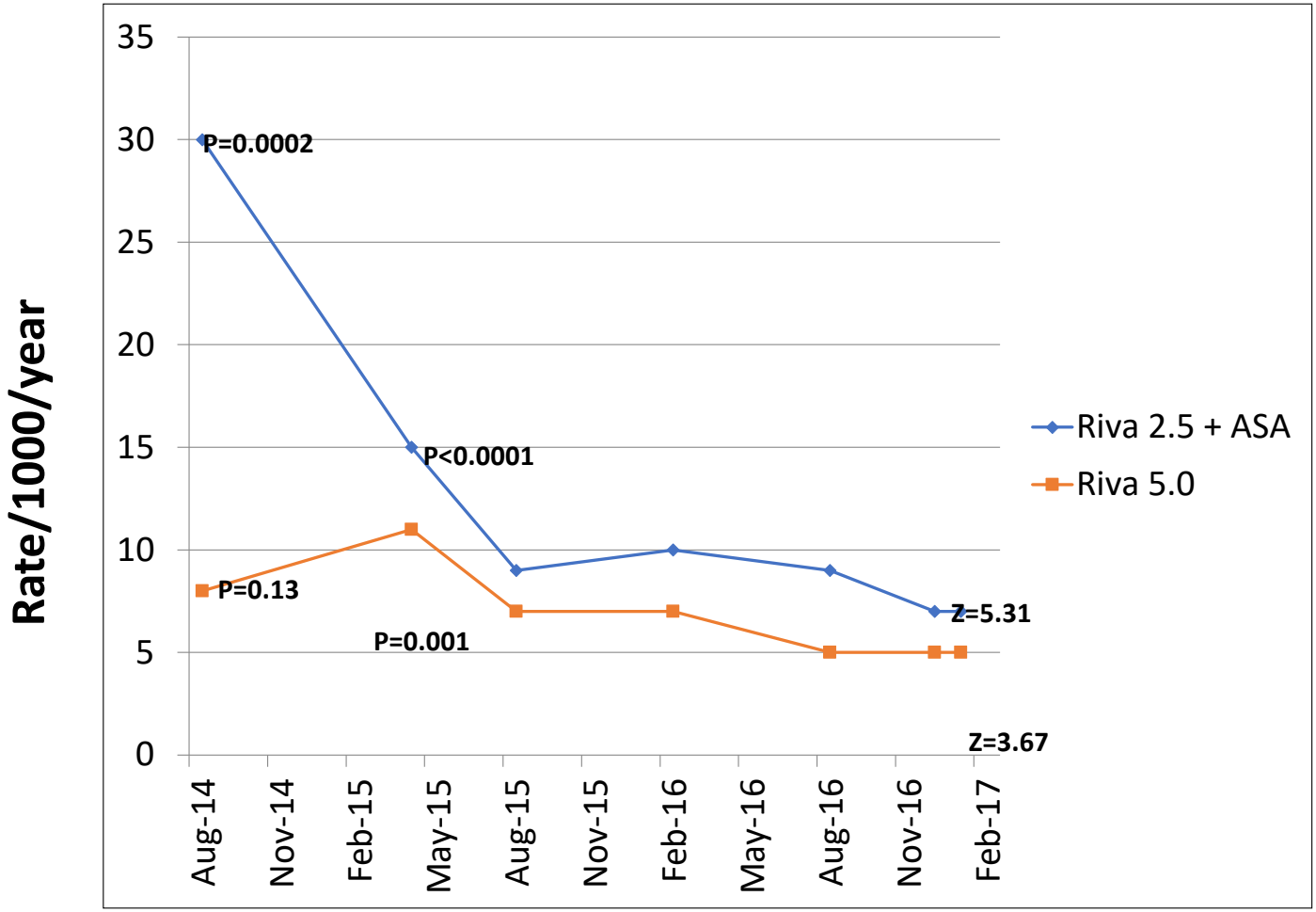
Primary: CV death, stroke, MI



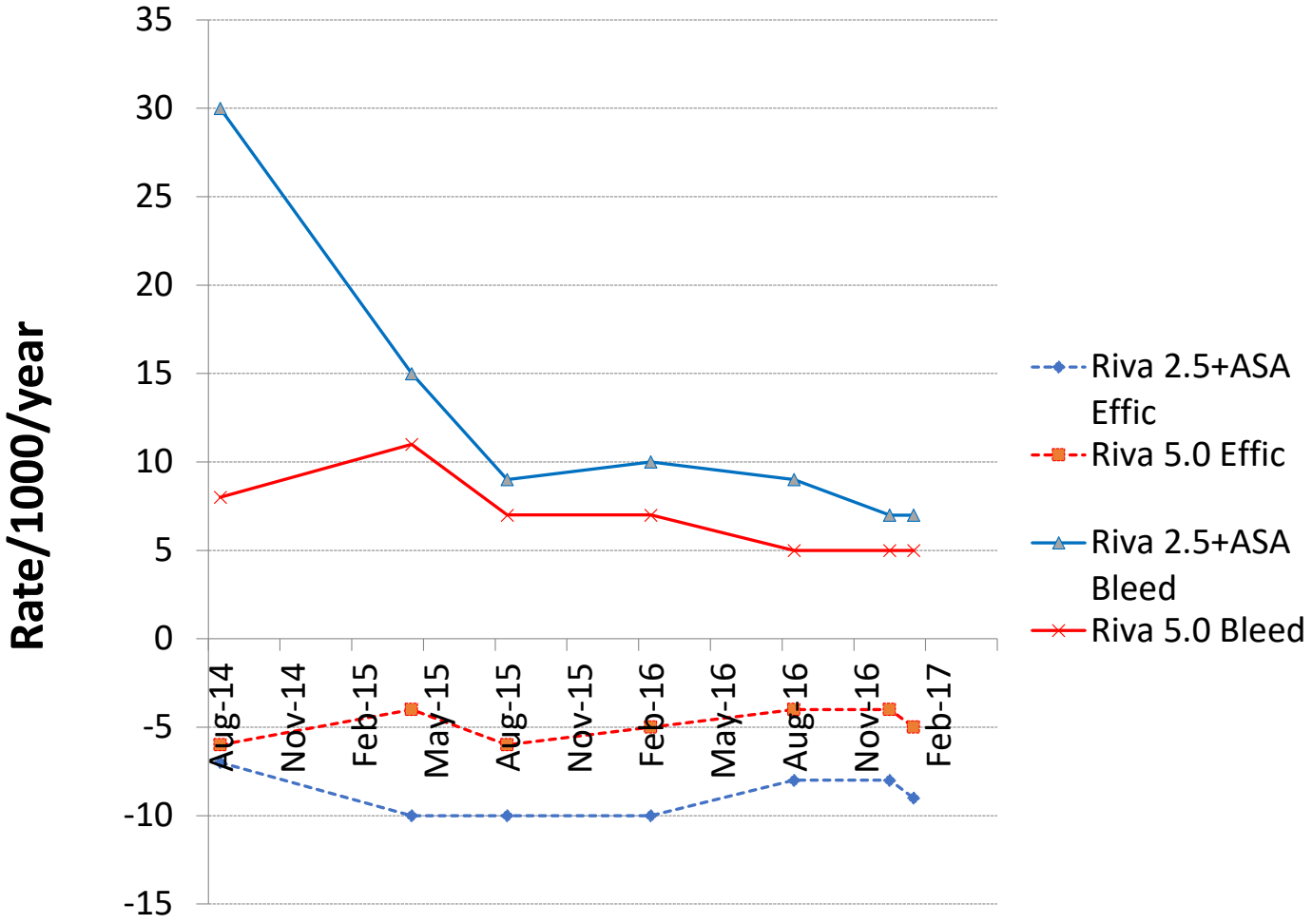
Stopping Guidelines

Safety

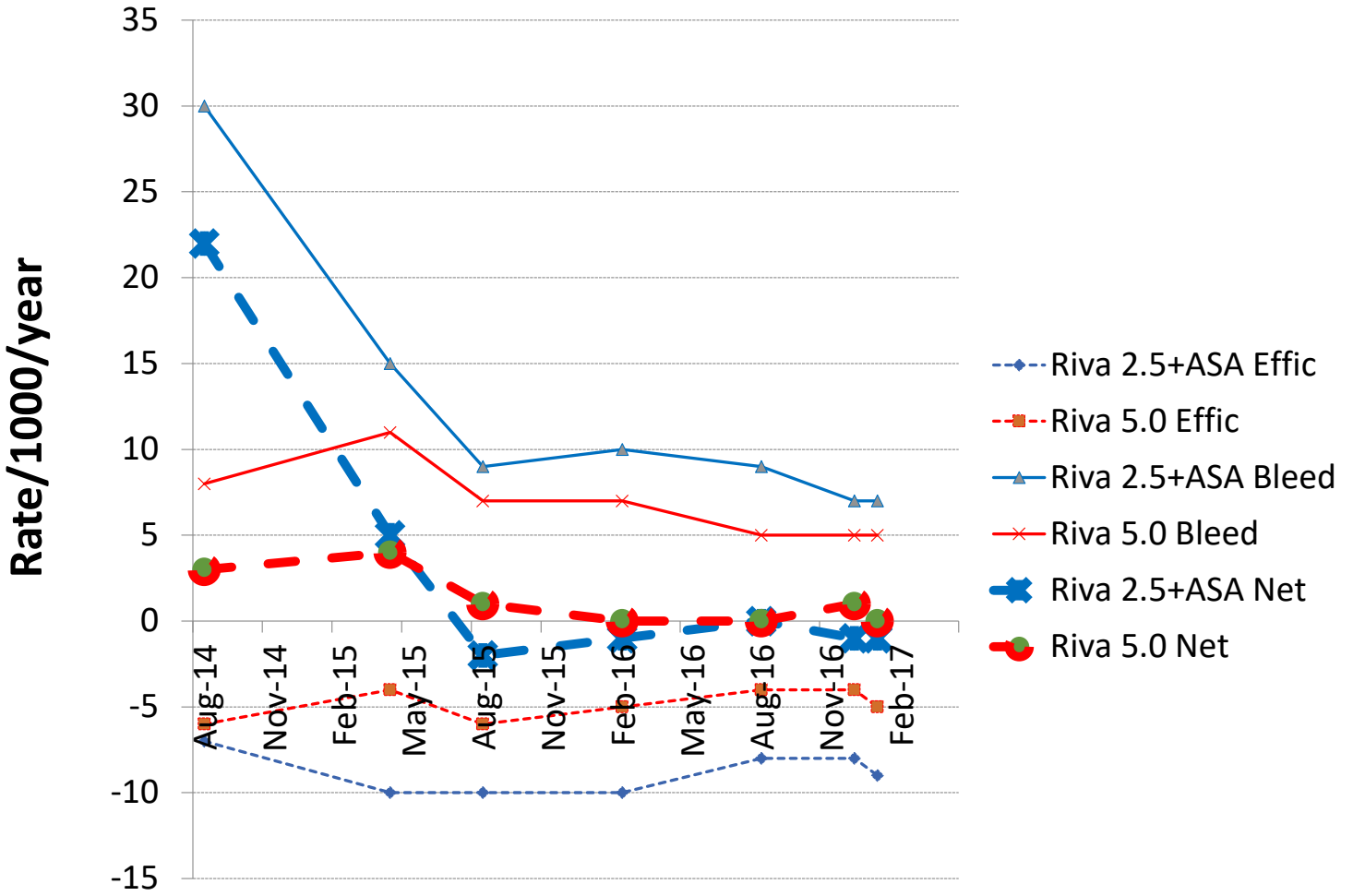
The DSMB will review safety outcomes ….
with special attention to **bleeding events** and events of special interest.
No formal boundaries will be used for terminating the study for safety reasons,
but clear and consistent evidence of net harm that overrides any benefit should be apparent.
As a guide the DSMB will review the incidence of the
primary efficacy outcomes (composite of CV death, stroke, myocardial infarction) and
compare it to the incidence of the **primary safety outcome** (modified ISTH major bleeding).
In the case that risk outweighs benefit in these two important outcomes, the DSMB may recommend that the study be stopped early for “harm”.



Absolute Excess Major Bleeding
Riva/ASA vs ASA and Riva vs ASA



Absolute Excess Major Bleeding and Reduced Primary Outcome Riva/ASA vs ASA and Riva vs ASA

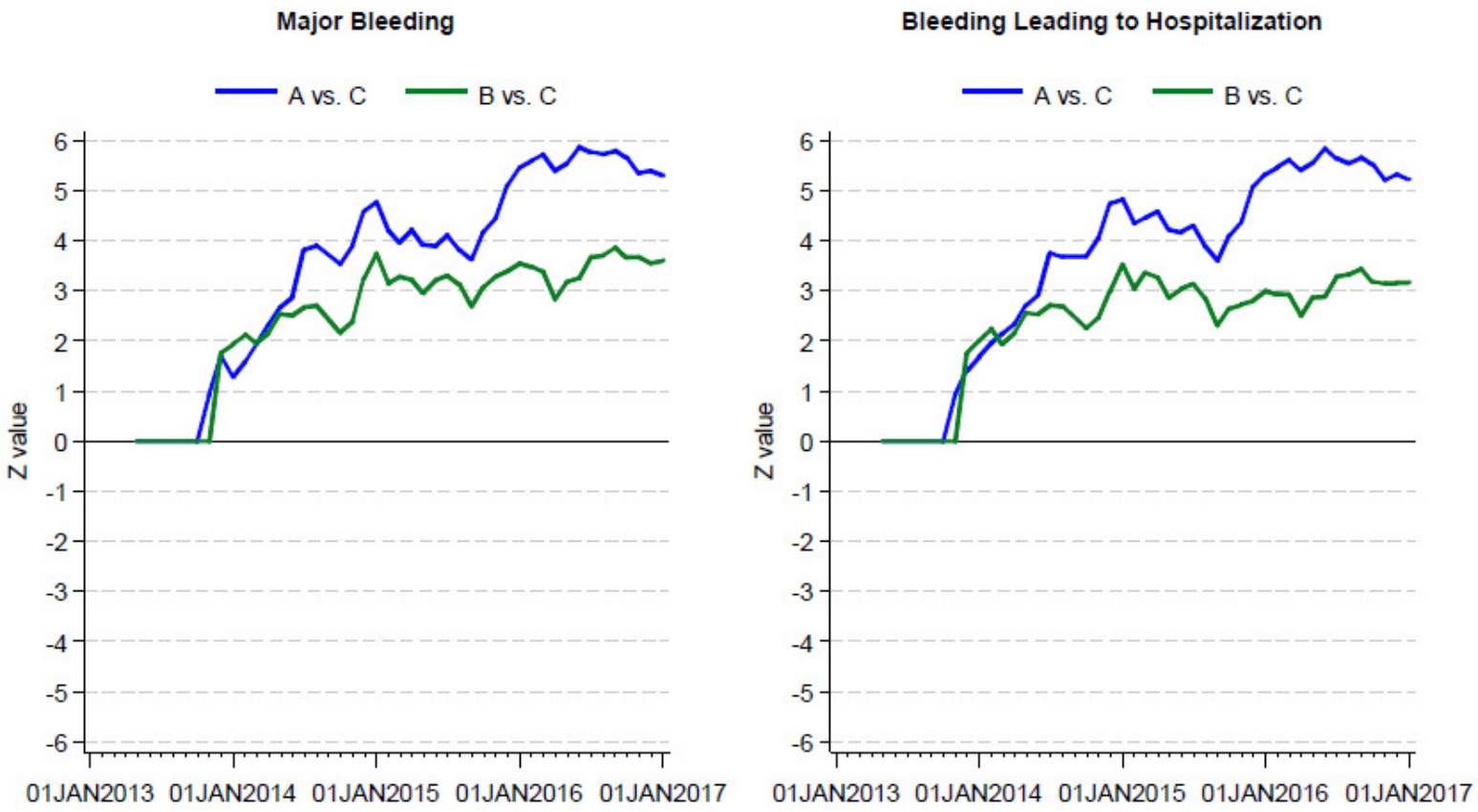


Aggregate Major Bleed caused + Primary outcome prevented
Riva/ASA vs ASA and Riva vs ASA

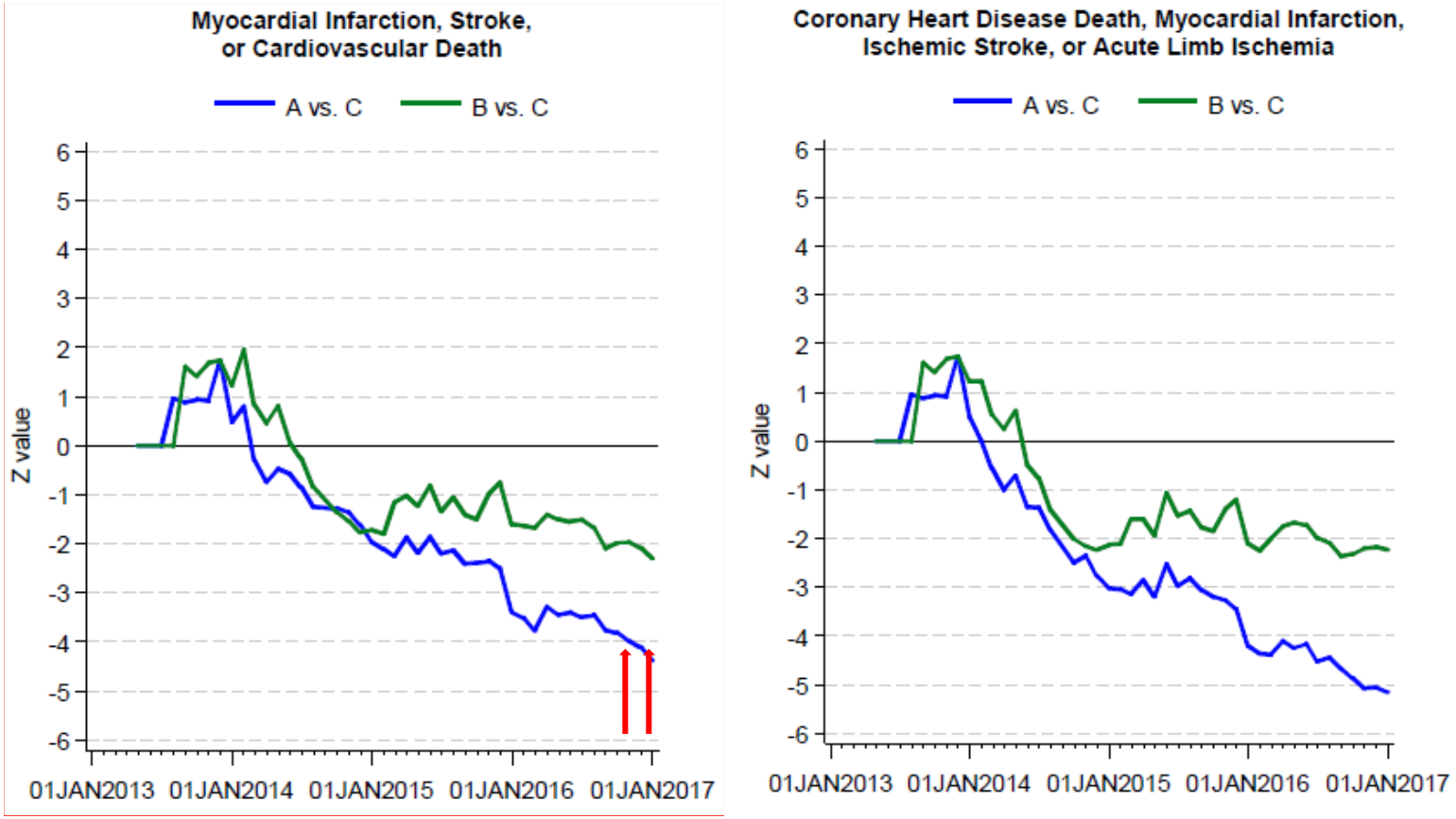
Stopping Guidelines

Efficacy

The DSMB is responsible to monitor for greater than expected efficacy. The DSMB will review both verified and locally determined events but will, in general, **prioritize verified over locally determined assessments.**
The DSMB's meeting for the **First Scheduled Interim Analysis for Efficacy** will occur when **approximately 50% (i.e., 1100) of the total 2200 subjects with primary outcome events** have accrued. For this First Scheduled Interim Analysis for efficacy, the primary outcome will be monitored using a modified Haybittle-Peto boundary of **4 standard deviations**. The boundary refers to a treatment difference that is greater than the prescribed number of standard errors and that favors rivaroxaban. In the analysis of the primary outcome this corresponds to a one-sided p-value < 0.0001 for the primary comparisons performed with a stratified log-rank test.
Second interim analysis…



Z-values for differences in bleeding rates



Z-values for differences in outcome rates

Outcome	Rivaroxaban plus Aspirin (N=9152)	Rivaroxaban Alone (N=9117)	Aspirin Alone (N=9126)	Rivaroxaban plus Aspirin vs. Aspirin Alone	
				Hazard Ratio (95% CI)	P Value
	number (percent)				
Primary outcome: CV death, stroke, or myocardial infarction†	379 (4.1)	448 (4.9)	496 (5.4)	0.76 (0.66–0.86)	<0.001
Net-clinical-benefit outcome: CV death, stroke, myocardial infarction, fatal bleeding, or symptomatic bleeding into critical organ	431 (4.7)	504 (5.5)	534 (5.9)	0.80 (0.70–0.91)	<0.001

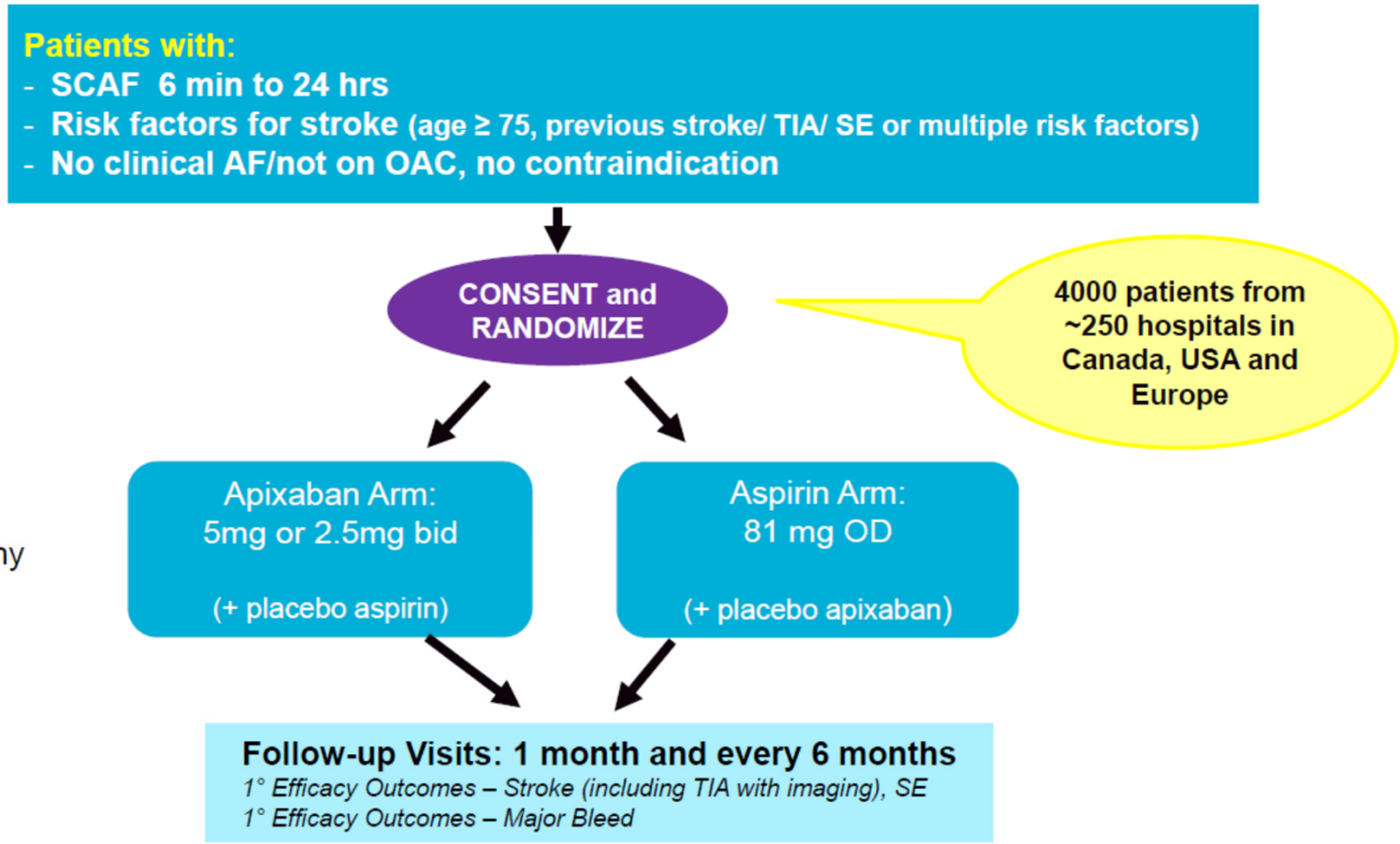
Monitoring Emerging Data From the COMPASS Trial of an Antithrombotic Agent

John A. Cairns, MD,[a] John W. Eikelboom, MB, BS,[b] Olga Shestakovska, MSc,[b] Salim Yusuf, DPhil,[b] David DeMets, PhD[c]

J Am Coll Cardiol 2019; 73: 2769-72.

DSMC

ARTESiA Study Design



Double-blind, double-dummy design

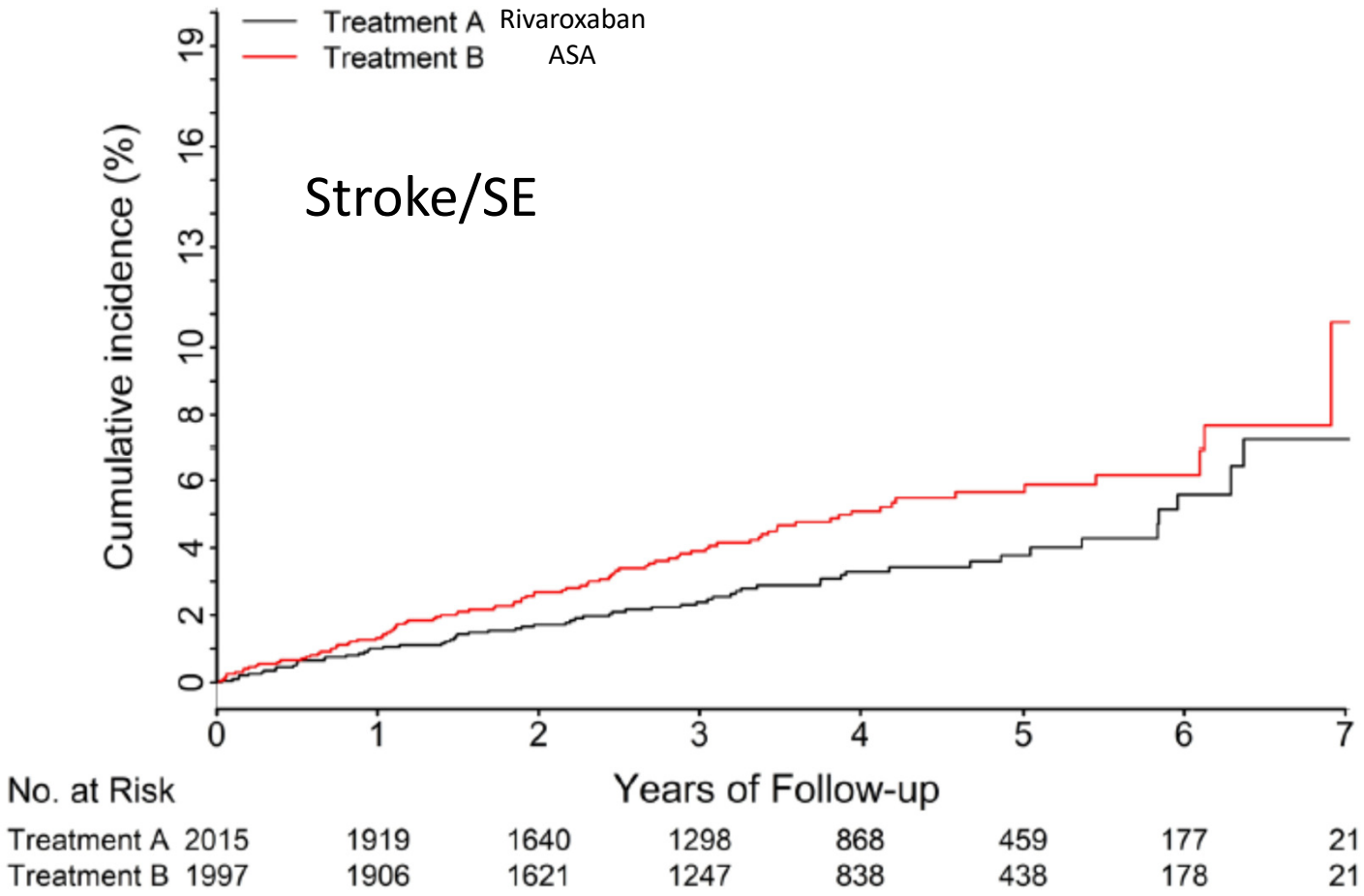
Stopping Guidelines

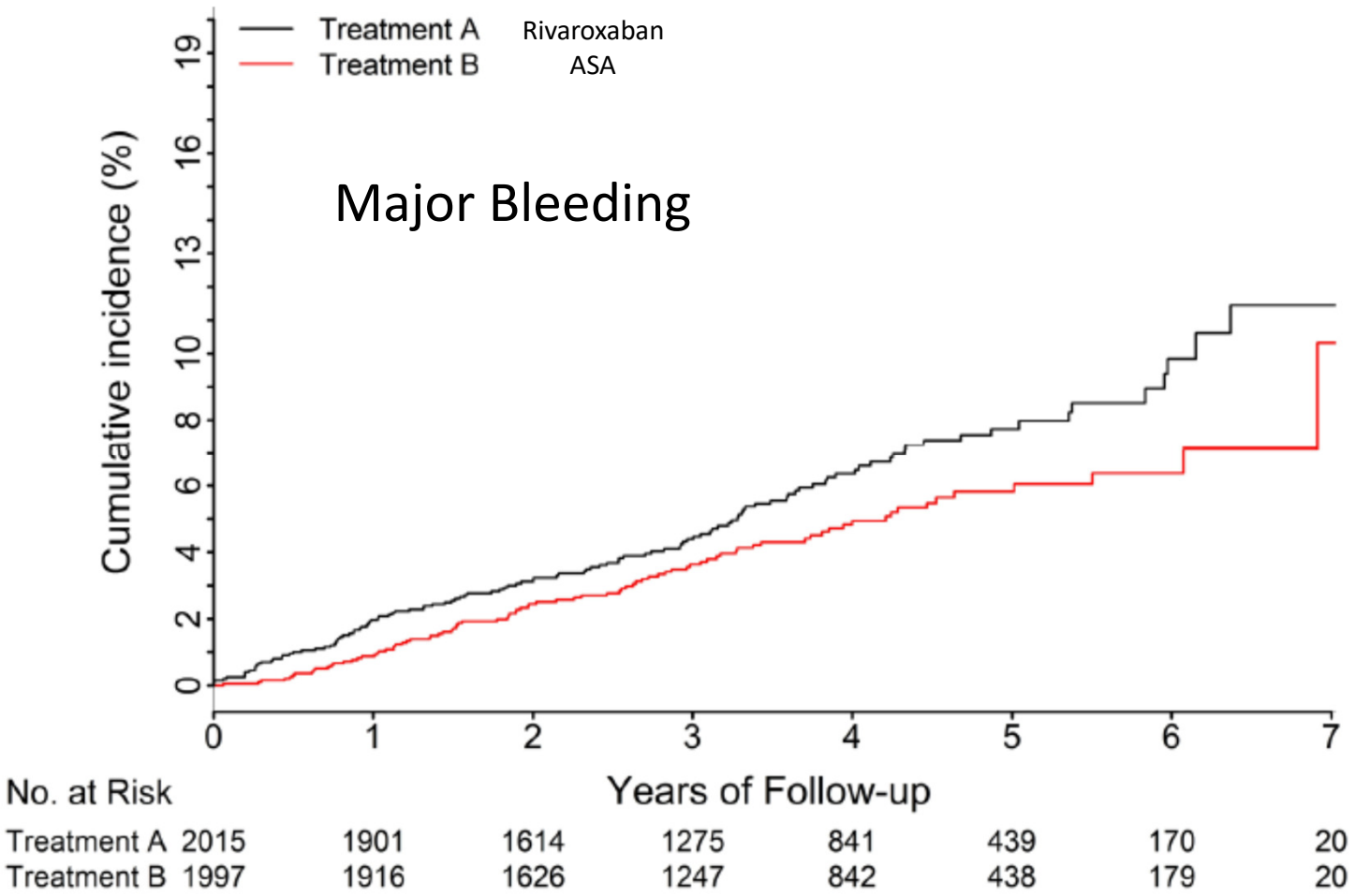
Efficacy

The DSMC is responsible to monitor for greater than expected efficacy. The DSMC will review both adjudicated and locally determined events but will, in general, prioritize adjudicated over locally.

The planned formal interim efficacy analyses will occur once 82 (1/3 of total events) and 164 (2/3 of total events) primary efficacy outcome events have occurred.

The modified Haybittle-Peto rule will be used to guide the decision regarding early stopping: a reduction of 4 standard deviations ($\alpha = 0.00006$) in the analysis of the primary outcome at the first interim analysis or 3 standard deviations ($\alpha = 0.0027$) at the second interim analysis. If the monitoring boundary is crossed at either of the 2 interim analyses, a second look will be conducted after at least 3-6 months to confirm the boundary remains crossed and that the trend in treatment effect is not temporary.


Treatment A Rivaroxaban
Treatment B ASA
Stroke/SE
Cumulative incidence (%)
0
2
4
6
8
10
13
16
19
0
1
2
3
4
5
6
7
Years of Follow-up
No. at Risk
Treatment A 2015 1919 1640 1298 868 459 177 21
Treatment B 1997 1906 1621 1247 838 438 178 21


Treatment A
Treatment B
Rivaroxaban
ASA
Major Bleeding
Cumulative incidence (%)
0
2
4
6
8
10
13
16
19
0
1
2
3
4
5
6
7
Years of Follow-up
No. at Risk
Treatment A 2015 1901 1614 1275 841 439 170 20
Treatment B 1997 1916 1626 1247 842 438 179 20

DSMC Monitoring

Excess of major bleeds on Riva noted very early in trial

Request for quantitation of severity of strokes and of major bleeds

June 2020 - **First** formal **interim analysis** of efficacy

75 events (vs 84 in charter)

Riva vs ASA HR = 0.65 , Z = 1.82 (4.0)

Major bleed HR = 1.59, p = 0.032

Composite of fatal stroke or symp ic bleed, less on riva

Composite of stroke/TIA or major bleed HR = 1.16

(no double count of ic bleeds)

All cause mortality and vascular mortality no difference

April 2023 – **Second** Formal **interim analysis** of efficacy

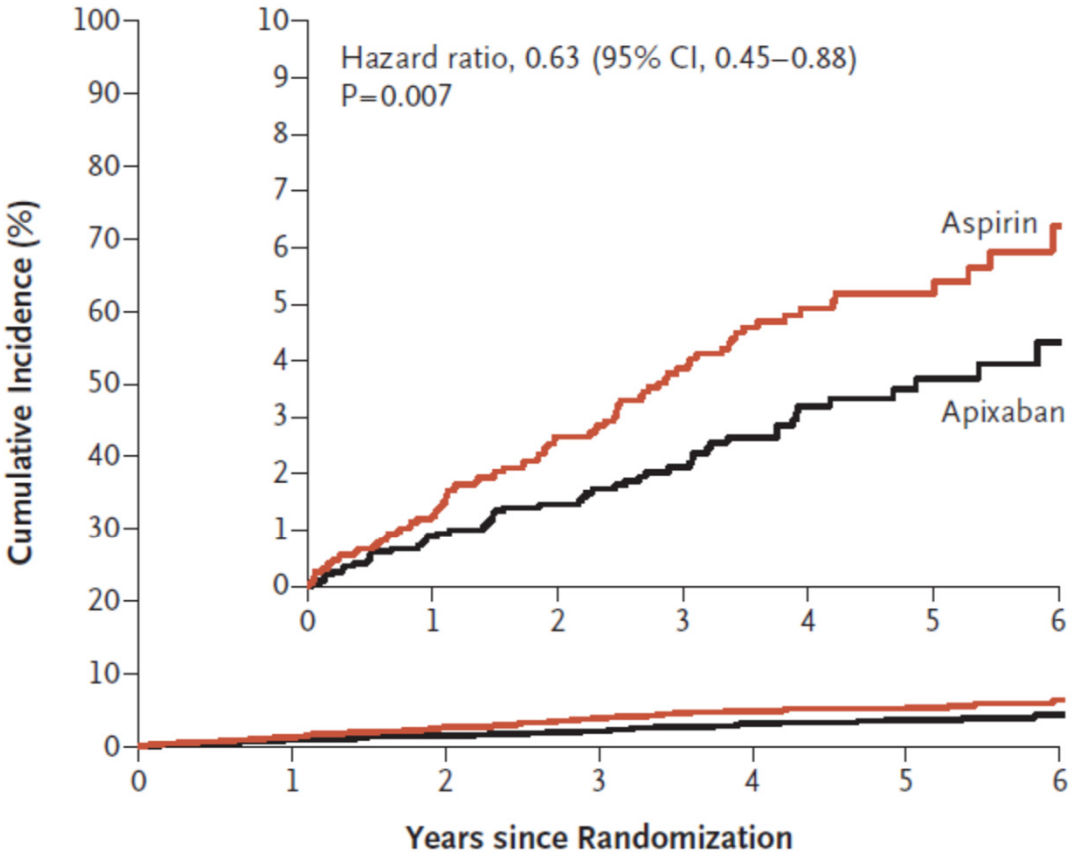
154 events (vs 164 in charter)

Riva vs ASA HR = 0.68, Z = 2.36 (3.0)

Major Bleed HR = 1.36, p < 0.05

Composite of Major stroke/TIA + major bleed HR = 1.03

All cause mortality and vascular mortality no difference



No. at Risk

Aspirin	1997	1777	1539	1120	780	468	200
Apixaban	2015	1786	1558	1157	820	474	214

Figure 1. Stroke or Systemic Embolism (Primary Efficacy Outcome).

N Engl J Med 2024;390:107-117

Outcome	Apixaban (N=2015)		Aspirin (N=1997)		Hazard Ratio (95% CI)	P Value
	no. of patients with event	*%/patient-yr*	*no. of patients with event*	*%/patient-yr*		
Stroke or systemic embolism	55	0.78	86	1.24	0.63 (0.45–0.88)	0.007
Stroke	55	0.78	84	1.21	0.64 (0.46–0.90)	
Ischemic or unknown type†	45	0.64	71	1.02	0.62 (0.43–0.91)	
Hemorrhagic	10	0.14	13	0.18	0.76 (0.33–1.73)	
Severity according to score on modified Rankin scale‡						
0–2	31	0.44	45	0.65	0.68 (0.43–1.07)	
3–6	19	0.27	37	0.53	0.51 (0.29–0.88)	
Missing data	5	0.07	2	0.03	2.48 (0.48–12.80)	
Systemic embolism	0		2	0.03	NA	
Major bleeding¶	106	1.53	78	1.12	1.36 (1.01–1.82)	0.04
Fatal bleeding	10	0.14	14	0.20	0.70 (0.31–1.57)	
Symptomatic intracranial hemorrhage	17	0.24	23	0.33	0.73 (0.39–1.36)	
Gastrointestinal bleeding	55	0.78	31	0.44	1.76 (1.13–2.74)	

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Gastrointestinal bleeding	55	0.78	31	0.44	1.76 (1.13–2.74)	

Among patients with subclinical atrial fibrillation, apixaban resulted in a lower risk of stroke or systemic embolism than aspirin but a higher risk of major bleeding.

In this trial involving patients with risk factors for stroke who were found to have subclinical atrial fibrillation, apixaban resulted in a lower risk of stroke or systemic embolism than aspirin. This effect included a substantial between-group difference in disabling or fatal stroke. The risk of major bleeding was higher with apixaban than with aspirin; most cases responded readily to supportive care.

Conclusions
Abstract
Paper